An open-label, phase I/II safety, pharmacokinetic, and proof-of-concept study of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (CRPC)

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Disclosures

Karim Fizazi: participation to advisory boards for Orion, Astellas-Medivation, Janssen
Items to be covered

- Background
- Nonclinical data
- Androgen receptor antagonist dose escalation study (ARADES)
  - Phase I dose escalation part
  - Phase II expansion part with 200mg, 400mg and 1400mg *total daily doses*
    - Given as 100mg bid, 200mg bid, 700mg bid; in the morning and evening
- Conclusions
Androgen receptor activation in CRPC
ODM-201 has a unique profile

- No CYP inhibition or induction with therapeutic doses

<table>
<thead>
<tr>
<th>Compound</th>
<th>AR affinity Ki (nM)</th>
<th>Antagonism WT AR IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>78</td>
<td>155</td>
</tr>
<tr>
<td>ARN-509</td>
<td>53</td>
<td>168</td>
</tr>
<tr>
<td>ODM-201</td>
<td>9</td>
<td>65</td>
</tr>
<tr>
<td>ORM-15341 (main metabolite)</td>
<td>8</td>
<td>25</td>
</tr>
</tbody>
</table>

*Refs. Clegg et al, Cancer Research 2012; Forster et al, Prostate 2011

** Rat autoradiography (QWBA confirms brain/plasma ratio of 14C-ODM-201 related radioactivity was 0.04-0.06, indicating negligible penetration to the brain
Superior inhibition of tumor growth by ODM-201 in castration-resistant mouse VCaP xenograft model

VCaP:
- Derived from a bone metastasis of a patient with CRPC
- Contains endogenous (wild type, non-mutated) AR gene amplification and AR overexpression

**Tumor size (mm³, mean ± SEM)**

- Control
- ADT
- ADT+enzalutamide (20mg/kg qd)
- ADT+ODM-201 (50mg/kg qd)
- ADT+ODM-201 (50mg/kg bid)

Fizazi *et al.* ASCO GU 2013
**Phase I**

**Dose escalation**

ODM-201

n=24
(3 pts/dose level)

200 mg
400 mg
600 mg
1000 mg
1400 mg
1800 mg

**Objectives:**
- Tolerability - MTD
- PK, Efficacy

**Phase II**

**Dose expansion ODM-201**

n=110

200 mg, 400 mg and 1400 mg

**Objectives:**
- Define dose for further clinical trials
- Efficacy (PSA, CTCs, soft and bone lesions)
- Safety
- Exploratory biomarkers
- Explore various groups of CRPC pts
Key inclusion criteria

- Progressive mCRPC
  - S-testosterone level < 0.50 ng/ml
- Chemotherapy-naïve or ≤ 2 prior chemotherapy regimens
- Prior CYP17-inhibitor therapy allowed
- Obligatory prior use of an AR inhibitor (bicalutamide, etc)

Key exclusion criteria

- Prior therapy with enzalutamide or any investigational AR antagonist
- Patients with history of seizures or at risk of seizures were not excluded
ARADES phase I results

- n=24 pts
- No dose limiting toxicity
- Excellent tolerability:
  - most common events mild to moderate: asthenia, diarrhea and nausea
  - mainly cancer related
- Anticancer activity detected over all doses
- At 12 weeks, 81% of pts had a ≥ 50% PSA decrease
- Pharmacokinetics linear up to 1400 mg
From phase I to phase II

- Three doses selected for phase II based on PSA response:
  - Two lowest effective daily doses (200 mg and 400 mg) selected during the phase I part
  - Highest tolerable, PK-linear, dose (1400 mg) selected after phase I (PK plateau at 1800 mg)
- Explore different subgroups of CRPC pts (previously treated or not with chemotherapy and CYP17 inhibitors)
Demography for ARADES phase I/II

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Chemo-/CYP 17i-naïve (n = 37)</th>
<th>Post-chemo/CYP 17i-naïve (n = 32)</th>
<th>Post-CYP17i (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median years, range)</td>
<td>73 (55-83)</td>
<td>67 (53-82)</td>
<td>69 (55-89)</td>
</tr>
<tr>
<td>Baseline PSA (median ng/mL, range)</td>
<td>101 (2.7-1294)</td>
<td>94 (8.4-663)</td>
<td>139 (8.9-5000)</td>
</tr>
<tr>
<td>Baseline CTC count ≥ 5</td>
<td>47%</td>
<td>45%</td>
<td>49%</td>
</tr>
<tr>
<td>Disease localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>86%</td>
<td>84%</td>
<td>87%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>51%</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Visceral</td>
<td>27%</td>
<td>26%</td>
<td>31%</td>
</tr>
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</table>

Pts from Phase I with daily doses of 600 (n=3), 1000 (n=4) and 1800 (n=3) mg are not detailed in the table.
PSA response at 12 weeks

Chemotherapy and CYP17i-naïve

Post-chemotherapy/ CYP17i-naïve

Post-CYP17i

≥50% PSA decrease: 65%  32%  9%

≥30% PSA decrease: 71%  52%  20%

At 1400mg dose:
6/7 pts (86%) had a ≥50% PSA decrease

*Data truncated at +25%
CTC response at 12 weeks

Chemotherapy/CYP17i-naive

Post-chemotherapy/CYP17i-naïve

Post-CYP17i

N=5 stable favorable (count 0>0), not shown on figure

N=6 stable favorable (count 0>0), not shown on figure

N=6 stable favorable (count 0>0), not shown on figure

*Data truncated at +25%
Most common (<10%) toxicities by grade

<table>
<thead>
<tr>
<th>Follow-up until week 12</th>
<th>No of patients (%) (N=124)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Fatigue /Asthenia</td>
<td>30 (24%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Pain</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12 (10%)</td>
</tr>
</tbody>
</table>

- No clear evidence that any of the toxicities observed are drug related
- No seizures during study treatment
  - One not related case was reported 27 days after stopping treatment (patient was on 200 mg bid for 87 days until disease progression)
- Safety profile after longer treatment period remains similar
Acknowledgements

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